Altery and alienance in neuroscience: Jurg Zutt "Reloaded"

Giuseppe Di Iorio¹  
Sjoerd J.H. Ebisch¹  
Giovanni Martinotti¹,²  
Massimo di Giannantonio¹  

¹ Department of Neuroscience, Imaging and Clinical Sciences, University “G.d’Annunzio”, Chieti-Pescara, Italy  
² Department of Pharmacy, Pharmacology, Postgraduate Medicine, University of Hertfordshire, Herts, UK

Address for correspondence:  
Giuseppe Di Iorio  
Department of Neuroscience, Imaging and Clinical Sciences,  
University “G. d’Annunzio”  
Viale Amendola 47  
66100 Chieti-Pescara, Italy  
E-mail: giudiorio1@gmail.com

Abstract

In recent years, neuroscientific research into the brain bases of the self and its socio-relational nature has been conducted by experimental models of functional neuroimaging. In this editorial are explored the correspondence between the semantic anthropo-phenomenology of the German psychiatrist Jurg Zutt (1893-1980), and recent neuroscientific theories. In particular, we discuss the theoretical correlation between the concept of “Internal Attitude,” as dealt by Zutt, and aberrant functioning of brain networks involved in self-related processing including the default mode network, the salience network and sensorimotor networks in patients with schizophrenia when solicited by socio-relational stimuli. The aim of this editorial is not only to propose a synthesis between the anthropological and neuroscientific perspectives, but, above all, to invoke a language that takes into account the human being in unison with the complexity of its neural

KEY WORDS: Zutt, anthropo-phenomenology, self, default-mode-network, internal attitude.

Introduction

The purpose of this editorial is to explore the correspondence between the semantic anthropo-phenomenology of the German psychiatrist Jurg Zutt (1893-1980), and recent neuroscientific theories. In particular, we discuss the theoretical correlation between the concept of “Internal Attitude,” as dealt by Zutt, and aberrant functioning of brain networks involved in self-related processing including the default mode network, the salience network and sensorimotor networks in patients with schizophrenia when solicited by socio-relational stimuli. The idea consists of a “back to the past”: starting from the past and hypothesize correspondences, not yet revealed, with the latest scientific evidence.

The anthropological sense of Jurg Zutt’s psychiatry and the concept of “inner attitude”

In the 1920s, influential psychopathologists in continental psychiatry including Jurg Zutt, Eugene Minkowski and Ludwig Binswanger suggested that, in the case of the mentally ill, the clinic should not only seek for correspondences between signs and functioning of the central nervous system, but that psychopathology should also seek to understand the meaning of symptoms from an anthropological point of view. Using Minkowski’s words: “Where can we find the human and how can we recognized it” (1). This was possible through the consideration of the developments in philosophy that in those years put the intentional activity of consciousness towards the world at the center of its efforts. Thus, by this enlargement of the horizon of psychiatry, anthropo-phenomenological psychiatry was born aiming at directing its efforts to constantly confront the essence of the psychopathological phenomenon, i.e. the psychological connections between symptoms, and to challenge the reality that it encloses.

Zutt had no doubt that anatomy (especially neurological anatomy), physiology (especially pathology of metabolism), and pharmacology had an essential place within basic psychiatric science. The former two mainly concern the study of the genesis of psychoses related to brain degeneration, whereas the latter regards toxic psychoses. In concrete cases, all are integrated by psychopathology in the form of descriptions of profound analyses.
At that time, descriptive psychopathology had provided therapeutic approaches of great value for endogenous psychoses. However, in Zutt’s opinion, a satisfactory understanding of these pathologies still had not been achieved. Zutt invited his colleagues to look with less scepticism at the help that contemporary ontology could offer them to properly clarify psychopathological problems, because the task of psychiatry is to “show the fundamental contents of the lived life, which can already be found in the very first stages of human development” (2). According to Zutt, psychiatry has to put the lived body in the world at the center of its inquiries, which is not a body naturally endowed with functions, but a pre-reflective body that “I am before any intellectual realization on it” (2).

In the 1950s and 1960s, Zutt assembled his most important contributions in a collection titled Über Daseinsstörungen, in Auf dem Wege einer anthropologischen Psychiatrie (2).

The first of these essays is entitled “The Internal Attitude - A Psychological Analysis and Its Significance for Psychopathology, Especially for Schizophrenia”. Zutt argues that the “internal attitude is the state of consciousness that allows us to voluntarily inform another person about our personal experience and transposing, voluntarily, the reverse phenomenon”. He also wrote: “[...] the inner attitude and the voluntary movements that depend upon it constitute, with the adult bodily form and the perceivable sensory processes of the autonomic nervous system, the most important source of the knowledge of lived alterity, and the only way to voluntarily convey our personal experience to others”. We could therefore depict Zutt’s concept of inner attitude as a kind of diaphragm, a thin tympanum interposed between the emotional/cognitive “frequencies” of the self as the “historical narrative” (the profoundly constitutive structure of personality) and the purely sensory ones emerging from environmental stimuli (both exogenous and endogenous). The inner attitude, in relation to changing environmental stimuli, would be the conscious and expressive actualization of the self in a bodily sense and, mainly, in a motor sense by producing coherent responses both to the fundamental constitutive structure of the individual and to the worldly instances that constantly require adaptations. Starting from his model, and representing a substantial re-proposition of Mikowsky’s concept of schizophrenic autism (3), Zutt sees the genesis of schizophrenic disorder as an interrupted communication between ipseity and the inner attitude that results in a sort of “primary” deafness of the self to environmental and social stimuli. In line with the construct of Binswanger, such a “Pathology of the Will” would produce the alienation of the self whose outward manifestation of being-with-each-other becomes constantly incongruous and bizarre (4).

Neuro-scientific hypotheses on endophenotypes regarding the social skills

In recent years, neuroscientific research into the brain bases of the self and its socio-relational nature has been conducted by experimental models of functional neuroimaging according to different, but complementary, perspectives on the self and self-other relationship.

On the one hand, the intrinsic self, defined as a “self-perceived image of one’s inner world”, is found to be supported by the default mode network (DMN) and the salience network (5). Brain regions in the DMN are particularly active during spontaneous thought or resting states and link the self with personal narrative and information about transient physiological bodily states. The DMN and the salience network, which can be explored through functional magnetic resonance imaging (fMRI), are based on a structural “core” consisting of the anterior and posterior cingulate cortex, medial prefrontal cortex, temporal-parietal junction, and insula (6, 7). Northoff and Stanghellini (8) argued that DMN spontaneous activity would produce, at a pre-phenomenal level, the space-temporal plot – what Karl Jaspers would call “Nude Reticulate” (9) – providing meaning to (or rather a sense of) subjective experiences at the phenomenal level (including relationality).

On the other hand, an extrinsic self, defined as self-experience in sensation and action based on dynamic and intentional bodily interactions with the environment, is mediated by multisensory integration, self-monitoring, and predictive processes in the sensorimotor system (10-12). Two main aspects of the extrinsic self can be distinguished: the sense of ownership (of one’s body, perceptions, and thoughts) and the sense of agency (the experience of being the source of one’s own actions and their consequences) (13).

Intriguingly, intrinsic and extrinsic self-networks are also involved in the relation between the self and its social environment. Sensorimotor networks include the mirror neuron network allowing one to share the experiences of others, whereas the DMN and insula integrate internally generated and affective information about self and others (14).

A vast amount of evidence shows that both intrinsic and extrinsic components of the self are disrupted in schizophrenia (7, 12, 15). Moreover, based on a review of evidence from neuroimaging research (16), it was recently proposed that especially abnormal functional interactions between these components could play a key role in the pathophysiology of symptoms in schizophrenia: altered interactions between intrinsic and extrinsic self-networks probably disrupt the sense of self as well as interaction of the self with its social environment. This perspective parallels Jurg Zutt’s concept of “the inner attitude and the voluntary movements that depend upon it” (2) clearly emphasizing the intentional relation between the inner self and the environment that supplies the self with exogenous and endogenous (social) stimuli.

For instance, fMRI results in patients with schizophrenia, compared to healthy control participants, showed an abnormal relationship between internal self-experiences and empathically shared feelings of others. The findings implied a reduced awareness of the dis-
tinction between self and non-self, due to aberrant functional connectivity between the posterior cingulate cortex, premotor cortex and posterior insula (17, 18). A subsequent fMRI study demonstrated that, whereas in healthy control participants functional connectivity of ventromedial prefrontal cortex in the DMN during a resting state predicted neural activity during a social perception task in somatosensory regions in medial parietal cortex, in schizophrenia this resting-state relation was disrupted (19). Altogether, these findings indicated that an impaired socio-relational self in schizophrenia could be traced to dysfunctional modulation of intrinsic and extrinsic self-networks in the brain.

Jurg Zutt “Reloaded”

With this editorial, we invite you to recall the evolution of psychopathological semantics and what G.E. Berrios calls a "paradigm effect": the necessity to refer to a phenomenon according to the normative “language” of a certain historical moment (20). Through the “functionalistic” view of modern neuroscience, we hypothesise a semantic correspondence between a theoretical problem, particularly that of the internal mental dynamics that govern the affective interaction with other individuals, and the language of Zutt’s anthropological psychopathology. Zutt possibly foresaw far more than he could empirically demonstrate when he assumed a kind of disconnection and stiffening of the inner attitude at the basis of autistic functioning in schizophrenia.

In fact, the same condition seems to correspond to a failure in the functional modulation of self-related neuronal networks in response to social stimuli. Moreover, the functional linkage gap between brain networks of internal self-processing and external self-processing, both contributing to socio-relational aspects of the self, seems to be a re-edition (in the optics of the “imaging phenotype”) of the disconnection between the empirical world and the self constitutive structure that, as hypothesized by Zutt, modulates the inner attitude. In conclusion, we approach the problem of inter-subjective communication in schizophrenia neither as a simple anatomo-functional substratum of social skills nor as a pure enunciation of the anthropological foundation of the “mit-daisen”. We would rather ask to reflect on the possibility of investigating the structure of the “anatomo-functional substrate of being anthropologically destined for relationality”. Our intent is not only to propose a synthesis between the anthropological and neuroscientific perspectives, but, above all, to invoke a language that takes into account the human being in unison with the complexity of its neural connections.

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Cocaine addiction and gender differences: treatment difficulties

Emilio Sánchez-Hervás
Addictive Behaviors Unit of Catarroja, Valencia Regional Health Departament, Spain

Address for correspondence:
Emilio Sánchez-Hervás
Addictive Behaviors Unit of Catarroja
Av. Rambleta 14
46470 Catarroja, Valencia, Spain
E-mail: esh455k@gmail.com

Abstract
Cocaine use is an important public health problem and in recent years more and more research aimed at improving the effectiveness of treatments is being done. Although the literature has shown evidence of gender differences in the development and maintenance of cocaine use disorders, there are still some knowledge gaps that prevent conclusive statements regarding how such differences affect the outcomes of the treatment. Research on gender differences is necessary because it can help to identify differential factors that allow better care and treatment strategies for this type of patients. A review of the results of the most recent research on the subject is carried out, and the implications and difficulties for the treatment of such differences are discussed.

KEY WORDS: cocaine, woman, substance use disorder, gender, treatment.

Introduction
Cocaine is one of the most commonly consumed drugs in the world. Its consumption causes important psychological, physical and social outcomes, as well as an important economic and social burden (1). Therefore, in many countries, the development of effective treatments for the treatment of cocaine use disorders is a priority in public health policies (2).

Cocaine stimulates the central nervous system by increasing the normal activity of certain brain neurotransmitters. They fundamentally excite the action of noradrenaline, serotonin and dopamine. Basically the action of cocaine focuses on two processes: a) promotes a greater amount of endogenous neurotransmitters and b) blocks the physiological reuptake of these neurotransmitters, preventing their reabsorption into the neuron (3). The psychological and behavioral effects induced by the use of cocaine depend on several factors: the route of administration, the chronicity of its use, the health of the user, the past and present consumption of other drugs and alcohol, and the environment where the substance is consumed. The purer the substance is, the greater the specific neurobiological and behavioral effects will be. Cocaine is usually adulterated with other substances such as mannitol, lactose or glucose to add weight and, with caffeine, lidocaine, amphetamines, quinine or even heroin, to add flavor and provide additional stimulant effects to the central nervous system. Both the concentration of cocaine and the adulterants affect the response of the subject to the use of the substance (4).

Cocaine is the most commonly used illicit stimulant drug in Europe. Among regular consumers, a broad distinction can be made between more socially integrated users, who often sniff powder cocaine, and marginalised users, who inject cocaine or smoke crack (cocaine base). It is estimated that 17.5 million European adults (aged 15 to 64) (5.2% of this age group) have used cocaine at some point in their lives. Among them there are some 2.3 million young adults aged 15 to 34 (1.9% of this age group) who have used the drug during the last year. Cocaine was cited as the primary drug by around 63,000 clients entering specialised drug treatment in 2015 and by around 28,000 first-time clients. 14% of all the consumers who initiate treatment are women (5).

Recent literature shows the existence of differences in the development and maintenance of cocaine use disorders among men and women. Gender differences can influence responses to consumption of cocaine and the course and maintenance of the addiction (6-9). These differences may have important implications for treatment, although it is not known with certainty how they affect the final results. Since addiction to drugs in general and to cocaine in particular has traditionally been considered as a male problem, research on gender-related differences in...
cocaína uso ha sido escaso. Aunque todavía existe un estigma asociado y más prejuicio contra las mujeres que usan cocaína, existe un mayor reconocimiento en los últimos años. Estas mujeres tienen más acceso a cocaína que las hombres que usan, lo que significa que la ingesta de cocaína ha aumentado con el paso del tiempo, y como consecuencia, el número de mujeres en los servicios de tratamiento ha aumentado.

Las diferencias de género no son únicas a los perfiles dependientes de cocaína, pero también se observan en grupos dependientes de otras sustancias (11), tanto en muestras de población general (12, 13). Un artículo cuyo objetivo es identificar diferencias de género en el consumo de cocaína en adictos es presentado. El estudio de las diferencias de género puede ayudar a identificar factores diferenciales para mejorar la atención y el tratamiento de la cocaína, y define diferentes indicadores prognósticos. Por lo tanto, diferentes tipos de factores podrían ser la base de estas diferencias.

**Neurobiological factors**

Los factores neurobiológicos podrían contribuir a las diferencias de género en la adicción a cocaína. El número de neuronas dopaminérgicas, la densidad de terminaciones dopaminérgicas, así como la reactividad de los sistemas dopaminérgicos (involucrados en el rendimiento y el control motivacional), varían entre hombres y mujeres, y han sido mostrados para ser modulados por los estrógenos, especialmente los estrógenos (10).

Aunque las fluctuaciones hormonales en las mujeres son raras, la relación entre la dosis de estrógenos y progestágenos en mujeres puede variar en relación con su ciclo menstrual. Un estudio sugiere que la sensibilidad a la cocaína puede variar en relación con el ciclo menstrual. Los estrógenos pueden mediar la respuesta a la cocaína (15), ya que la administración de estrógenos puede mejorar las propiedades de recompensa de la cocaína, lo que tiene la capacidad de disminuir los síntomas de abstinencia de cocaína (16, 17).

Los estudios preclínicos señalan que los sexos difieren en el reconocimiento y mantenimiento de la cocaína administrada (18, 19), y sugieren que a las mujeres les es más fácil auto-administrar más cocaína que a los hombres (20). En un estudio reciente (21), se confirmó que cuando los niveles de estrógenos aumentaron, las mujeres auto-administraron más cocaína. Los autores sugieren una posible relación entre los estrógenos y las cocaína craves.

Aunque, en términos del proceso de reglamentación, el ciclo menstrual no ha sido definitivamente vinculado con este proceso, la posibilidad de ajustes fisiológicos en el procesamiento de recompensa se ha elevado (14). También se ha sugerido que las poblaciones femeninas experimentan cambios más drásticos en los niveles hormonales (pubertad, embarazo y menopausia) que las mujeres con el riesgo de desarrollar problemas relacionados con la cocaína (22).

Algunos estudios han demostrado que las mujeres pueden ser más sensibles a menudo a la cocaína que a las sustancias que inducen el estrés (23). El estrés aumenta la demanda de cocaína y contribuye al retraso. Las mujeres pueden ser más afectadas por el estrés (22), y el aumento de la actividad del sistema nervioso central puede interactuar con otros sistemas de neurotransmisores, como la dopamina y la serotonina (14). Las cocaína dependientes pueden beneficiarse con intervenciones que reduzcan el ansiedad y la demanda de cocaína (24).

En resumen, se ha propuesto que los desequilibrios hormonales pueden contribuir a las diferencias de género en la adicción, ya que son modulados por las hormonas (27). Para algunos autores, una mejor comprensión del papel de los sexos en la adicción puede ayudar al desarrollo de estrategias preventivas y terapéuticas (28, 29).

**Factors related to the course of addiction**

Las mujeres cumplen los criterios diagnósticos para el trastorno de consumo de cocaína más rápido (20) y entran en programas terapéuticos antes que los hombres. Este rápido avance hacia la adicción se conoce como "telescoping" (30). Mientras que los hombres inician el consumo de cocaína para sentir placer o energía, las mujeres comienzan a consumir cocaína para aliviar problemas preexistentes psicopatológicos. La estrategia maladaptiva de auto-administración sigue el curso más rápido de la adicción y entra en programas de tratamiento más rápidamente que los hombres (10)

Las mujeres experimentan menos euforia y más ansiedad que los hombres (31), y muestran una mayor severidad de los síntomas de abstinencia a la cocaína (32). Muestran una mayor sensibilidad a las condiciones (2), 27, 34-36).

En términos de características anteriores, las mujeres presentan más empleo, estatus socioeconómico, problemas familiares y psiquiátricos, y menos problemas legales (37). Las mujeres tienen una historia más breve de uso de sustancias, menos años de uso regular de cocaína. Tienen un historial más corto de tratamiento, una frecuencia menor de consumo de alcohol antes del consumo de cocaína. Tienen un historial menos común para el tratamiento de los trastornos del consumo de cocaína (38). Es más común que las mujeres se presenten a la cocaína para aliviar preexistente (28, 29).

Las mujeres sufren más severamente problemas físicos y psicológicos, y tienen más dificultades para dejar de fumar. También tienen un mayor número de comorbidades, como las depresiones (38), trastorno de ansiedad (39), trastorno obsesivo-compulsivo (33), trastorno de ansiedad (40) y en general, una mayor marginación en varios ámbitos (41). El uso de cocaína en mujeres parece afectar el riesgo de presentar más síntomas de estrés postraumático (PTSD) (42). Los pacientes con uso de cocaína deben ser tratados como pacientes sin tratamiento.
cocaine use disorder (43). However, they are less likely than men to meet the criteria for antisocial personality disorder or attention deficit hyperactivity disorder (13). Women are more likely to attribute relapse to negative emotional states and interpersonal conflicts (44). Many women engage in high-risk sexual behaviors which leads to an increased risk for HIV infection or other STDs, and report increased sexual compulsion (45).

Factors related to the treatment

Women have lower rates of substance use and dependence than men and represent a minority of participants in substance use treatments. Given this situation, clinical trials are more representative of men's response to treatment (13). In the literature on the results of cocaine treatment, gender analyzes are not usually reported. While it is reasonable to expect that all validated treatments will be useful for all populations, the external validity of existing studies remains a significant problem in this regard (46). Women seeking treatment have more severe cocaine addiction problems than men and present a more significant mismatch in various areas of their lives (41, 47). Women have traditionally been considered to be more committed to treatment, have more positive attitudes, higher expectations of success (42, 48), and they further comply with the therapeutic indications of professionals (49). But women tend to be more vulnerable than men in terms of treatment outcomes (16, 25). They have more anxiety and craving symptoms during treatment, which increases the likelihood of using cocaine to reduce anxiety symptoms. The greater psychological severity and greater mismatch in women is associated with lower retention of treatment and worse outcomes (50).

The literature on gender and outcomes of cocaine treatment is limited and mixed. Biological differences may affect the response to certain treatments more than others. For example, women appear to be more vulnerable to side effects induced by medications used to treat addiction (51). Several studies do not find gender differences in behavioral treatments in cocaine-dependent samples (36, 37, 52). However, differences have been found in pharmacological treatments; for example, a worse response of disulfiram in women (53). These inconsistent results on treatment response are often attributed to methodological issues, differences in patient characteristics, and different types of treatments.

In general, women show poorer therapeutic progress than men with similar addiction histories, which may indicate the advisability of performing additional specific interventions to promote better outcomes (54). For example, health-related needs (pregnant women, mothers) appear to differ by sex (55, 56), as well as the higher incidence of comorbid psychiatric disorders (33, 38), so the establishment of treatment priorities should also reflect these differences (50).

Demographic differences in treatment entry (the greater likelihood that women have children, are unemployed, have difficulties in accessibility, greater stigma and lower social support), also affect treatment needs, complicate sustained commitment to treatment and are cited as reasons for gender-specific adaptations (35, 40, 52-55, 57-60). Special mention should be made of pregnant women, who may suffer from an isolation problem when trying to hide their addiction, fearing possible legal or social consequences (61).

Finally, some data suggest that gender differences also exist in adolescents with cocaine abuse, in the course of the disorder and in the response to treatments (62). Biological factors, psychiatric comorbidities and environmental factors present specific gender risks when adolescents (63) and young adults (64) begin to initiate substance use. It has been documented, for example, that young women may use cocaine and other drugs seeking an anorexic effect (65), or that young women attending treatment services have higher psychosocial problems rates than their male counterparts (66). Given the paucity of work in this area, epidemiological studies are needed to identify the specific gender differences of this subpopulation (17).

Discussion and conclusions

Cocaine addiction is a complex disorder where neurobiological, psychological, social and cultural factors interact. Cocaine, at moderate doses, causes activating effects on the brain. This action translates into an elevation of mood, energy and alertness. These effects are immediate after consumption and perfectly objective after doses of 100 milligrams of intranasal cocaine. Once the addiction is developed, the interruption of the consumption produces withdrawal syndrome (anxiety, depression, emotional lability ...) (67). Women experience less euphoria and more anxiety than men, and they show a greater severity of the symptoms of early withdrawal such as anxiety, tension, difficulty concentrating and irritability. In Europe, women who start treatment for cocaine dependence account for 14% of the total (5). Treatment services were designed for men, as they have formed the majority of users of care services for problems related to cocaine use. On the other hand, different studies show that offering additional services to address specific gender needs can improve the outcomes of traditional treatments (68, 69). These specific needs for women include, among other things (70, 71): medical services, health promotion, psychoeducation, attention to cultural and linguistic needs, stress reduction training and coping skills, family and child related services, integral case management, mental health services, services for people with disabilities and personal development programs.
An important issue, still unresolved is the extent to which treatments should be gender specific, and also to what extent men can benefit from their own specific treatment format (42). Few treatment programs for cocaine addiction offer specialized services for women, and their effectiveness has not been fully evaluated yet. A recent study reports that adding gender-sensitive services to traditional treatment requires smaller additional resources and there are no differences in cost-effectiveness compared to traditional treatment (72).

The integrated programs are designed for gender differences by providing treatment for substance use as well as services to address other maternal needs. The components of the treatment programs for women include prenatal care, child care, workshops addressing women’s issues, mental health care, and comprehensive health care (73), all in a sole medical care area. Despite the growth of integrated programs, there is a lack of a common theoretical framework, which has led to a considerable heterogeneity of programs and hampered the evaluation of their effectiveness (56). In view of this it can be said that the lack of specific services for women is widespread, and the way in which gender affects retention and treatment outcomes is uncertain.

Limitations and future directions

Among the limitations of our work, there is a tendency to ignore gender-based analyzes, information on gender-specific problems is limited, as well as the interpretation of the results of the existing studies. It should be also mentioned the scarcity of specific research on treatment outcomes for cocaine in women. The sex differences found in the literature also indicate the need to recruit an adequate number of female subjects in preclinical and clinical studies to improve our knowledge about cocaine abuse in women (51). The needs additional to those of their addiction require a more complete service provision. A greater offer of care services would enable the improvement of effectiveness and greater access and retention in treatment. The knowledge provided by research could be used to develop specific actions in the areas of health promotion, prevention, evaluation, treatment, continuous care and interdisciplinary coordination, through the application of intervention procedures that have been validated for both sexes (31, 45, 74, 75). It would be desirable to increase the empirical data with systematic and specific approaches (76), orienting research to the study of effective treatments for each particular subgroup of patients (77).

This paper has explored some of the special circumstances related to cocaine-dependent women. It was not intended to carry out a comprehensive review of the literature, but rather an attempt to show the current picture and the scientific and clinical data on the subject. Recent research has shown that a number of factors contributes to gender differences in both development and maintenance of cocaine use disorders. Although there are still important gaps in knowledge, especially those related to specific treatment modalities that may be more effective, such differences should be considered by clinicians, practitioners and health managers, which would allow the development and implementation of more effective intervention strategies in assisting women with cocaine addiction problems, based on the evidence available to date.

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Cocaine addiction and gender differences: treatment difficulties


The impact of depot and long acting injectable antipsychotics on serum levels of brain-derived neurotrophic factor in schizophrenic and schizoaffective patients: results of a 24-month longitudinal prospective study

Mirko Manchia1,2  
Diego Primavera1,3  
Luca Deriu1  
Edoardo Caboni1  
Novella Iaselli1  
Davide Sundas1  
Massimo Tusconi1  
Roberto Collu3  
Maria Scherma3  
Alessio Squassina3  
Donatella Congiu3  
Paola Fadda3,4  
Walter Fratta3,4  
Bernardo Carpiniello1

1 Section of Psychiatry, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy  
2 Department of Pharmacology, Dalhousie University, Halifax, Nova Scotia, Canada  
3 Division of Neuroscience and Clinical Pharmacology, Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy  
4 Centre of Excellence “Neurobiology of Dependence”, University of Cagliari, Cagliari, Italy

Address for correspondence:  
Bernardo Carpiniello  
Section of Psychiatry  
Department of Medical Sciences and Public Health, University of Cagliari  
Via Liguria 13  
09127 Cagliari, Italy  
Tel.: +3907041518  
Fax: +39070480083  
E-mail: bcarpini@iol.it

Abstract

Introduction: Schizophrenia (SCZ) and schizoaffective disorder (SAD) are severe and complex psychiatric disorders whose liability threshold is likely modulated by the interplay of biological, mainly genetic, and environmental factors. Consistent evidence has pointed to the role of serum brain-derived neurotrophic factor (BDNF) as a plausible illness biomarker in SCZ-spectrum disorders. There is no consensus, however, on the temporal trajectory of this decline. The decrease of peripheral BDNF could be constant, with premorbid levels roughly similar to those detected in unaffected individuals, linearly declining during the course of the illness. Alternatively, BDNF peripheral levels might fluctuate in association with acute psychopathological phases of the disorder. In this context, we sought to investigate the longitudinal variation of serum BDNF levels over 24 months in a cohort of Sardinian patients [Longitudinal Assessment of BDNF in Sardinian Psychotic patients (LABSP)]. Here, we present a secondary analysis of LABSP data, focusing on the impact of antipsychotic therapy, particularly depot and long-acting injectable (LAI), on the longitudinal trajectory of serum BDNF levels. Further, we tested whether genetic variation within the gene encoding for BDNF could moderate the relationship between BDNF serum levels and drug treatment.

Methods: LABSP patients were assessed every six months for a series of psychopathological, cognitive and drug-related measures, as well as for BDNF serum levels over 24-month. Blood samples for each patient were taken at the same time of the day (between 8:00 and 10:00 AM). BDNF serum levels were determined using BDNF ELISA Kit. Four tag single nucleotide polymorphisms (SNPs) within BDNF gene (rs1519480, rs11030104, rs6265 (Val66Met), and rs7934165) were selected using standard parameters and analyzed with Polymerase Chain Reaction (PCR). Mixed-effects linear regression models (MLRM) was used to analyze longitudinal data.

Results: Twenty-four patients out of 105 LABSP (22.9%) patients received therapy with depot/LAI. Analysis with MLRM showed a significant effect of depot/LAI treatment associated with increasing serum BDNF levels (Z = 1.9, p = 0.053). However, oral antipsychotics did not significantly impact on the longitudinal trajectory of serum BDNF levels (Z = 0.15, p = 0.9). There was no moderating effect of variants within BDNF gene on the identified association.

Conclusions: Our study identified a significant longitudinal increase of serum BDNF in SCZ and SAD patients treated with depot/LAI antipsychotic therapy. The identification of a significant impact of this preparation of antipsychotic treatment on serum BDNF despite the limited sample size,
points to a moderate to large magnitude of effect that should be investigated in future prospective studies.

KEY WORDS: antipsychotics, LAI, depot, complex disorders, longitudinal studies, biomarker.

Introduction

Schizophrenia (SCZ) is a severe, chronic mental disorder characterized by the presence of core psychopathological symptoms such as delusions and hallucinations (positive symptoms), impaired motivation and social withdrawal (negative symptoms), and cognitive impairment (1). As a complex disorder, the liability threshold for SCZ is likely modulated by the interplay of biological, mainly genetic, and environmental factors (2, 3). Indeed, family, twin and adoption studies have demonstrated the presence of a substantial genetic contribution to the risk of SCZ (4).

This has prompted molecular genetics studies, particularly genome-wide analyses, which have identified hundreds of genes significantly associated with the risk of SCZ (5). Similarly, schizoaffective disorder (SAD) has substantial heritability (6), and molecular studies suggest a specific influence of genetic determinants on its risk (7). In addition, as observed in SCZ, environmental factors appear to modulate the liability threshold for SAD determined by its genetic architecture (8).

In this context, researchers have attempted to take advantage of the increased knowledge on the genetic and biological make-up of these complex disorders to develop predictive risk models. One approach takes advantage of findings from genome-wide association studies (GWAS) and estimates the genetic correlation between pairs of complex traits using polygenic risk scoring (PRS) (9). For instance, SCZ-PRS associated significantly with decreased cognitive function in a large sample of older adults (10).

Another strategy consists of testing whether risk prediction in complex psychiatric disorders can rely on biomarkers, either based on neuroimaging or detectable in peripheral tissues such as serum, plasma or cerebrospinal fluid (CSF). Concerning the latter group, consistent evidence has pointed to the role of serum brain-derived neurotrophic factor (BDNF) as a plausible illness biomarker in SCZ-spectrum disorders (11, 12).

Indeed, there is consistent evidence that chronic and medicated SCZ patients (13-18), as well as first episode and medication naïve (19-23), present a significant decrease in serum BDNF levels compared to healthy individuals. However, the presence of discordant findings showing increased or unchanged BDNF serum levels in SCZ patients compared to healthy controls (24-27) prompted researchers to perform quantitative meta-analytical estimates. Indeed, Fernandes et al. (12) showed that SCZ is associated with a moderate decrease of serum and plasma BDNF levels compared to healthy controls.

There is no consensus, however, on the temporal trajectory of this decrease. The decrease of peripheral BDNF could be constant, with pre-morbid levels roughly similar to those detected in unaffected individuals, linearly declining during the course of the illness. Alternatively, BDNF peripheral levels might fluctuate in association with acute psychopathological phases of the disorder. Indeed, meta-analytical estimates have shown that BDNF decreases significantly in relation to illness activity (11). In addition, a critical factor modulating peripheral BDNF levels in SCZ-spectrum disorders is drug therapy. Quantitative data synthesis shows small but significant increases of serum BDNF levels under antipsychotic treatment (12), although existing studies have length of follow-up not longer than one year.

Another factor that might modulate variation in peripheral levels of BDNF in SCZ-spectrum subjects is genetics. Indeed, the Val66Met polymorphism of BDNF gene impacts activity-dependent secretion of BDNF (28). Thus, some studies have found that this functional variant can influence serum BDNF levels (29-31). Specifically, carriers of Met allele showed lower serum BDNF levels compared to those carrying Val allele (29, 30), although one study found the contrary (31).

In this context, we sought to investigate the longitudinal variation of serum BDNF levels over 24 months in a cohort of Sardinian patients [Longitudinal Assessment of BDNF in Sardinian Psychotic patients (LABSP)] (32). LABSP patients were assessed every six months for a series of psychopathological, cognitive and drug-related measures, as well as for BDNF serum levels (32). Here, we present a secondary analysis of LABSP data, focusing on the impact of antipsychotic therapy, particularly depot and long-acting injectable (LAI), on the longitudinal trajectory of serum BDNF levels. Further, we tested whether genetic variation within the gene encoding for BDNF could moderate the relationship between BDNF serum levels and drug treatment.

Subject and methods

Sample

The sample of SCZ and SAD patients was recruited at the community mental health centre of the Psychiatry Research Unit of the Department of Medical Science and Public Health, University of Cagliari and University of Cagliari Health Agency, Cagliari, Italy. The diagnosis of SCZ or SAD was confirmed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient Edition (SCID-I/P) (33) administered by trained mental-health professionals (psychiatry residents and/or senior clinical staff). Patients were recruited in LABSP if they fulfilled the following inclusion criteria: 1) age between 18 and 65 years; 2) diagnosis of SCZ or SAD according to DSM-IV-TR; and 3) stability during the six months before recruit-
ment. Exclusion criteria were: 1) refusal to provide consent; 2) presence of acute psychopathological symptoms; 3) presence of illness-related cognitive impairment of such severity that affects their ability to cooperate; 4) presence of major unstable medical illness; 5) severe mental retardation; 6) major neurological disorder or previous head injury; 7) current drug and alcohol dependence. Given the characteristics of the patient population followed-up at our community mental health centre, our sample was not comprised of drug-naive patients and was on a pharmacological treatment regime mainly based on antipsychotics.

**Assessment procedures**

Details of the assessment procedures have been previously published (32). Briefly, blood samples from recruited patients were taken at baseline (T_0), and at four consecutive time points: 6 months (T_1), 12 months (T_2), 18 months (T_3), and 24 months (T_4). Detailed information on ongoing pharmacological treatment regime was collected through direct assessment of the proband and an accurate review of available medical records.

**Sampling and assessment of BDNF serum levels**

Blood samples for each patient were taken at the same time of the day (between 8:00 and 10:00 AM). BDNF serum levels were determined using BDNF ELISA Kit (Booster Immunoleader, Cat. N° EK0307) for the quantitative detection of human BDNF in cell culture supernatants, serum and plasma. This kit is based on a standard sandwich enzyme-linked immuno-sorbent assay technology for specific quantifications of natural and recombinant human BDNF with a high sensitivity (< 2 pg/mL) and with no detectable cross-reactivity with other relevant proteins. After blood sampling, serum was allowed to clot in a serum separator tube for about 4 hours at room temperature. After that it was centrifuged at approximately 1000 X g for 15 min. Supernatant serum samples was collected in small aliquot and stored immediately at -20°C for future analysis. Then, samples were processed according to kit protocol and instructions. Optical density absorbance of each sample was read with a 450nm filter in a microplate reader (Thermo Scientific Multiskan FC) within 30 minutes after the final step of the kit procedure. Data obtained was processed according to kit protocol and instructions. Optical density absorbance of each sample was read with a 450nm filter in a microplate reader (Thermo Scientific SkanIt Software 3.0 for Multiskan FC).

**Genetic analysis**

Tag single nucleotide polymorphisms (SNPs) were selected using Tagger tool in Haploview (v4.2) based on linkage disequilibrium (LD), by including SNPs with $r^2 ≥ 0.8$, and with a minor allele frequency threshold of 0.01. Genotyping of the following BDNF SNPs rs1519480, rs11030104, rs6265 (Val66Met), rs7934165 was carried out using TaqMan probe on demand (C_11592757_20, C_1751792_10, C_11592758_10, C_11975676_10, Thermofisher) on a StepOne Plus instrument (Thermofisher). Primers were marked in VIC and FAM to discriminate between alleles. The reaction was carried out in 10 ul final volume, containing 5 ul of MasterMix (2X), 0.5 ul of probe assay (20X), 1ul of cDNA and 3.5 ul of RNA-free water. Polymerase Chain Reaction (PCR) settings were the following: 30 sec. 60°C, 10 min 90°C, and 40 cycles at 95°C for 15 sec and 60°C for 1 min.

**Data analysis**

Mixed-effects linear regression models (MLRM) was used to analyze longitudinal data (34, 35). Specifically, we regressed independent variables (both categorical and continuous) on BDNF serum levels (dependent variable). We used MLRM as this approach allows to model individual change over time and appears to be more flexible in terms of repeated measures, particularly when the number of observations per subject is not the same at each time point (34, 35). Further, these models allow generalization of non-normally distributed data for independent variables. We used MLRM to analyze the impact of oral antipsychotic and/or depot LAI therapy on the longitudinal variation of BDNF levels. Specifically, these independent variables were regressed on BDNF serum levels while correcting for age and sex. Finally, each BDNF SNP was added to MLRM as covariate while correcting for age and sex to check for a possible moderating effect. All data were analyzed using “lme4” package implemented in R (36). Missing data for independent variables was dealt with the “na.action” function implemented in R. The statistical significance of identified MLRM was calculated using the “multcomp” R package. Finally, graphical representation of MLRM was obtained with R packages “sjPlot” e “sjmisc”.

**Results**

**Sample characteristics**

The sample included 105 patients, 64 with a diagnosis of SCZ and 41 with SAD. The main clinical and demographic characteristics of the sample are detailed in Table 1. Relevant to this study is the number of subjects who were treated with oral antipsychotic therapy at the time of recruitment (T_0) (N = 103, 98%) and those who received therapy with depot/LAI over the course of the study (N = 24, 22.9%). Importantly, a proportion of patients treated with depot/LAI had concomitant oral antipsychotic therapy.

**The impact of oral antipsychotics and depot/LAI therapy on the longitudinal trajectory of serum BDNF levels**

Analysis with MLRM did not show a significant influence of treatment with oral antipsychotics on the longitudinal trajectory of serum BDNF levels (Model 1: $Z = 0.15$, $p = 0.9$) (Table 2). This was confirmed when we added sex and age as covariates (Model 2: $Z = 0.003$, $p = 0.9$). We then tested the effect of
Table 1. Main demographic and clinical characteristics of the LABSP sample.

<table>
<thead>
<tr>
<th>Variable (continuous)</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>105</td>
<td>48.85</td>
<td>10.45</td>
</tr>
<tr>
<td>Education, years</td>
<td>105</td>
<td>9.26</td>
<td>3.23</td>
</tr>
<tr>
<td>Offspring, N</td>
<td>105</td>
<td>0.34</td>
<td>0.95</td>
</tr>
<tr>
<td>Age of onset, years</td>
<td>105</td>
<td>21.77</td>
<td>9.30</td>
</tr>
<tr>
<td>Duration of illness, months</td>
<td>105</td>
<td>308.51</td>
<td>134.33</td>
</tr>
<tr>
<td>Age at first treatment, years</td>
<td>105</td>
<td>24.23</td>
<td>8.95</td>
</tr>
<tr>
<td>Duration of untreated illness, months</td>
<td>105</td>
<td>29.07</td>
<td>54.60</td>
</tr>
<tr>
<td>Antipsychotics, chlorpromazine equivalents, mg/die</td>
<td>103</td>
<td>378.92</td>
<td>272.3</td>
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<table>
<thead>
<tr>
<th>Variable (categorical)</th>
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<th>%</th>
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</thead>
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<tr>
<td>Sex (male)</td>
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<td>70.5</td>
</tr>
<tr>
<td>Age class</td>
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<td></td>
</tr>
<tr>
<td>18-20</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td>21-25</td>
<td>38</td>
<td>36.2</td>
</tr>
<tr>
<td>26-44</td>
<td>58</td>
<td>55.2</td>
</tr>
<tr>
<td>45-65</td>
<td>7</td>
<td>6.7</td>
</tr>
<tr>
<td>Marital status</td>
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<td></td>
</tr>
<tr>
<td>Single</td>
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<td>7.6</td>
</tr>
<tr>
<td>Married/Cohabitng</td>
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<td>9.5</td>
</tr>
<tr>
<td>Divorced</td>
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<td>1.9</td>
</tr>
<tr>
<td>Widowed</td>
<td>83</td>
<td>79.0</td>
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<tr>
<td>NA</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td>Presence of offspring</td>
<td>19</td>
<td>18.1</td>
</tr>
<tr>
<td>Employment</td>
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<td></td>
</tr>
<tr>
<td>Employed</td>
<td>7</td>
<td>6.7</td>
</tr>
<tr>
<td>Student</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Registered disabled civilian</td>
<td>95</td>
<td>90.5</td>
</tr>
<tr>
<td>Unemployed</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td>Presence of smoking</td>
<td>52</td>
<td>49.5</td>
</tr>
<tr>
<td>History of substance abuse</td>
<td>28</td>
<td>30.8</td>
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<tr>
<td>Current use of substances</td>
<td>5</td>
<td>5.5</td>
</tr>
<tr>
<td>Presence of family history of mental disorders</td>
<td>64</td>
<td>61.0</td>
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<tr>
<td>Long-acting antipsychotic therapy</td>
<td>24</td>
<td>22.9</td>
</tr>
</tbody>
</table>

NA: not available, SD: standard deviation.

depot/LAI therapy, identifying a marginally significant effect on serum BDNF levels over 24 months. Specifically, the subgroup of patients treated with depot/LAI had an increase in serum BDNF levels ($Z = 1.9$, $p = 0.053$). The strength of this association increased when the above covariates were included in the model ($Z = 2.2$, $p = 0.03$).

**Moderating effect of BDNF genetic variation**

In light of these results, we tested whether the four polymorphisms within BDNF gene might influence the impact of depot/LAI therapy on the longitudinal trajectory of serum BDNF levels. As shown in Table 3, no SNP significantly moderated the identified association. These models were tested without other covariates to avoid saturation of the MLRM.

**Discussion**

Our secondary analysis of LABSP data found that treatment with depot/LAI, but not with oral antipsy-
Table 2. Results of mixed-effects linear regression models.

<table>
<thead>
<tr>
<th>Model</th>
<th>Independent variable</th>
<th>Estimated coefficient</th>
<th>Standard error</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Time</td>
<td>-0.008</td>
<td>0.002</td>
<td>-5.0</td>
<td>6.3 x 10^{-7}</td>
</tr>
<tr>
<td></td>
<td>Oral antipsychotic</td>
<td>0.00001</td>
<td>0.00009</td>
<td>0.15</td>
<td>0.9</td>
</tr>
<tr>
<td>Model 2</td>
<td>Time</td>
<td>-0.008</td>
<td>0.002</td>
<td>-4.9</td>
<td>1.0 x 10^{-6}</td>
</tr>
<tr>
<td></td>
<td>Oral antipsychotic</td>
<td>-3 x 10^{-7}</td>
<td>0.00009</td>
<td>0.003</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>-0.002</td>
<td>0.003</td>
<td>-0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Model 3</td>
<td>Time</td>
<td>-0.08</td>
<td>0.02</td>
<td>-5.1</td>
<td>3.9 x 10^{-7}</td>
</tr>
<tr>
<td></td>
<td>Depot/Long-acting</td>
<td>0.11</td>
<td>0.06</td>
<td>1.9</td>
<td>0.053</td>
</tr>
<tr>
<td>Model 4</td>
<td>Time</td>
<td>-0.08</td>
<td>0.02</td>
<td>-5.0</td>
<td>6.7 x 10^{-7}</td>
</tr>
<tr>
<td></td>
<td>Depot/Long-acting</td>
<td>0.13</td>
<td>0.06</td>
<td>2.2</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>-0.004</td>
<td>0.003</td>
<td>-1.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

p, p-value.

Table 3. Mixed-effects linear regression models including BDNF genetic variants.

<table>
<thead>
<tr>
<th>Model</th>
<th>Independent variable</th>
<th>Estimated coefficient</th>
<th>Standard error</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Time</td>
<td>-0.08</td>
<td>0.002</td>
<td>-4.6</td>
<td>3.5 x 10^{-6}</td>
</tr>
<tr>
<td></td>
<td>Depot/Long-acting</td>
<td>0.19</td>
<td>0.07</td>
<td>2.7</td>
<td>0.006</td>
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<tr>
<td></td>
<td>rs7934165 A/G</td>
<td>0.05</td>
<td>0.07</td>
<td>0.7</td>
<td>0.5</td>
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<tr>
<td></td>
<td>rs7934165 G/G</td>
<td>0.02</td>
<td>0.09</td>
<td>0.2</td>
<td>0.8</td>
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<td>-4.7</td>
<td>2.9 x 10^{-6}</td>
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<td></td>
<td>Depot/Long-acting</td>
<td>0.17</td>
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<td>2.5</td>
<td>0.01</td>
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<tr>
<td></td>
<td>rs6265 (Val66Met) C/T</td>
<td>0.03</td>
<td>0.07</td>
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<td>0.6</td>
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<tr>
<td></td>
<td>rs6265 (Val66Met) T/T</td>
<td>0.01</td>
<td>0.11</td>
<td>0.06</td>
<td>0.9</td>
</tr>
<tr>
<td>Model 3</td>
<td>Time</td>
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<td>0.02</td>
<td>-4.7</td>
<td>3.1 x 10^{-6}</td>
</tr>
<tr>
<td></td>
<td>Depot/Long-acting</td>
<td>0.17</td>
<td>0.07</td>
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<td>0.02</td>
</tr>
<tr>
<td></td>
<td>rs1519480 C/T</td>
<td>0.09</td>
<td>0.3</td>
<td>0.3</td>
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<tr>
<td></td>
<td>rs1519480 C/T</td>
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<td>0.3</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Model 4</td>
<td>Time</td>
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<td>-4.7</td>
<td>3.3 x 10^{-6}</td>
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<td>0.07</td>
<td>2.5</td>
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<td>rs11030104 A/G</td>
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<td>0.06</td>
<td>0.9</td>
<td>0.34</td>
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<tr>
<td></td>
<td>rs11030104 A/G</td>
<td>0.05</td>
<td>0.1</td>
<td>0.4</td>
<td>0.6</td>
</tr>
</tbody>
</table>

p, p-value.

Antipsychotics, significantly impacted on the longitudinal trajectory of serum BDNF levels over the time of follow-up. Specifically, the 24 patients treated with depot/LA presented a longitudinal increase in serum BDNF levels. This finding is consistent with a number of preclinical (37-39) and clinical (12) studies. With regard to preclinical evidence, Park et al. (38) showed that chronic (21 days) treatment with quetiapine attenuated the hippocampal decrease of BDNF induced in rats through immobilization stress. These Authors subsequently suggested that this effect of antipsychotics on BDNF might be class-specific, with second-generation (aripiprazole and olanzapine), but not first-generation antipsychotics (haloperidol), effective in restoring the loss of BDNF induced by immobilization stress (39). This finding is partly concordant with the work of Pillai et al. (37), showing that striatal and hippocampal levels of BDNF in rats decreased after 90 days of treatment with haloperidol but were significantly restored after switching to a subsequent 90-day treatment with either olanzapine or risperidone. Indeed, other Authors have suggested that first- (haloperidol) or second-generation (risperidone) antipsychotics can reduce BDNF levels in rat brain (cortex and hippocampus) (40, 41). This discrepancy might be reconciled by taking into account antipsychotics dosage (42). Indeed, Chlan-Fourney et al. (42) observed that intermediate doses of risperidone had no effect on BDNF hippocampal levels in rats, suggesting that higher chronic doses of antipsychotics might determine long-term down-regulation of BDNF in the brain. Concerning clinical evidence, our results are consistent with the meta-analysis by Fernandes et al. (12) which analyzed 14 longitudinal
studies (total N = 463) showing that the use of antipsychotics was associated with a small but significant increase in serum and plasma BDNF levels. Of importance, this increase in BDNF serum and plasma levels was independent of treatment response [defined as at least 40% reduction in the Positive and Negative Symptoms Scale (PANSS) total score], but, differently from our work, was mainly led by studies showing a raise in plasma levels of BDNF rather than in serum (12).

Another finding of our secondary analysis is the discrepant effect of oral and depot/LAI antipsychotic therapy on serum BDNF levels. This might be explained by at least two factors: 1) the increased adherence among patients treated with depot/LAI intrinsic to the nature of this therapy, and 2) the specific pharmacokinetics of depot/LAI formulation. Concerning the first aspect, it is known that depot/LAI preparations have many advantages over oral therapy, such as not having to remember to take drugs daily, reducing the risk of unintentional or deliberate overdose, and transparency of adherence (43, 44). Secondly, depot/LAI have a more consistent bioavailability (43) and reduced peak-trough plasma levels (45) ensuring a more effective action of the drug centrally (43, 45). These factors can explain the presence of an increase in BDNF serum levels specific to the subgroup of patients receiving depot/LAI treatment in our study. Indeed, preclinical studies show that serum BDNF increases significantly in rats administered continuously (4-6 weeks which equals > 3 years in humans), but not intermittently, with risperidone (46). A final remark concerns the absence of a moderating effect of genetic variants within the BDNF gene on the significant impact of depot/LAI therapy on the serum levels of this neurotrophin. This is consistent with the quantitative data-synthesis of 13 studies performed by Terracciano et al. (47) showing that the Val66Met genetic polymorphism was not associated with BDNF serum levels, a finding corroborated by the GWAS analysis in a large cohort of Sardinian individuals (N = 2,054). Consistent with the high pattern of LD among the SNPs investigated in this study, no BDNF genetic variant significantly moderated the identified patterns of association. However, it is possible that the genetic effects of BDNF polymorphism on its serum levels are of such small magnitude that only studies with very large sample size will be able to detect a significant effect.

Our results should be interpreted in the context of several limitations. First, the subgroup of patients treated with depot/LAI has a limited sample size, a factor that hindered further secondary analysis (for instance testing an antipsychotic class-specific effect). However, it should be noted that the identification of a significant pattern of association between depot/LAI and serum BDNF in such a small subgroup of patients points to the presence of an effect size of moderate to large magnitude that should be investigated in future prospective studies. Secondly, given the limited sample size of the subgroup treated with depot/LAI, MLRM were run with a limited number of covariates to avoid saturation of models. Nevertheless, all tested models converged flawlessly suggesting their relative stability. Finally, it is possible that changes in a serum biomarker might not be representative of modifications at the brain level. However, the identification of a peripheral marker, such as serum BDNF, associated with a specific trait or phenotype, such as treatment with depot/LAI, might not necessarily provide with mechanistic insights on the pathophysiology of the disorder under study, but might rather be of prognostic utility in clinical settings.

Conclusions

In summary, our study identified a significant longitudinal increase of serum BDNF in SCZ and SAD patients treated with depot/LAI antipsychotic therapy. The identification of a significant impact of this preparation of antipsychotic treatment on serum BDNF despite the limited sample size, points to a moderate to large magnitude of effect that should be investigated in future prospective studies.

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Treatment with vortioxetine in outpatients with anxiety and depressive disorders: a retrospective analysis

Davide La Tegola1
Giulia Trotta1
Enrica Verrengia1
Enrico Biagi2
Manuela Caslini2
Fabrizia Colmegna2
Massimo Clerici1

1 Department of Medicine and Surgery, University of Milano-Bicocca, Milano, Italy
2 Mental Health Department, San Gerardo Hospital, Monza, Italy

Address for correspondence:
Davide La Tegola
Department of Medicine and Surgery,
University of Milano-Bicocca
Piazza dell’Ateneo Nuovo 1
20126 Milano (MI), Italy
E-mail: davidelategola@yahoo.it

Abstract
Vortioxetine is a novel antidepressant agent with multimodal action, combining serotonin transporter reuptake blockade and receptors modulation. This mechanism suggests a different antidepressant profile as compared with commonly used SSRIs / SNRIs. We investigated main clinical and demographic characteristics of subjects treated with vortioxetine. We retrospectively reviewed data of individuals attending San Gerardo Hospital outpatient clinic (“Ambulatorio Vademecum”) for anxiety and depressive disorders. We estimated a reduction in prescription of additional psychopharmacological treatments, in particular anxiolytics, in subjects treated with vortioxetine. In addition, vortioxetine was preferably used for the treatment of depression, as compared with anxiety and adjustment disorders. Since our data are preliminary and limited by important methodological issues, further studies based on a larger sample size, are needed to confirm the estimated trends.

KEY WORDS: vortioxetine, depression, anxiety.

Introduction
Anxiety and mood disorders are currently the most common mental illnesses in US and Europe, especially among primary care attenders (1). According to a recent report providing data on the current size of mental disorders for the EU countries, the 12 month prevalence in Europe is approximately 14% for anxiety disorders and 7.8% for mood disorders, dominated by major depression (6.9%) (2). Current guidelines recommend a long-term treatment for patients suffering from anxiety and mood disorders, in order to prevent relapses and recurrence (3). Several pharmacological and non-pharmacological options are available (4, 5). Antidepressant agents, such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and others (e.g. mirtazapine, bupropion, reboxetine, agomelatine), represent the core of the pharmacological approach (6). Vortioxetine has been approved for the treatment of adults with Major Depressive Disorder by the Food and Drugs Administration in September 2013 and the European Medicines Agency (EMA) in December 2013. Vortioxetine mechanism of action is related to its multimodal activity, combining direct serotonergic receptor modulation and serotonin transporter (SERT) inhibition (7). Moreover, vortioxetine is an antagonist at 5-HT3, 5-HT1D and 5-HT7 receptors, a partial agonist at 5-HT1B receptors and agonist at 5-HT1A receptors (8). Compared to placebo, vortioxetine is efficacious in the acute treatment (9) and long-term relapse prevention (10) of major depressive disorder. In this paper, we investigated the main clinical features of individuals who received an antidepressant treatment with vortioxetine, retrospectively reviewing data of subjects admitted to an outpatient service for anxiety and depressive disorders.

Materials and methods
We conducted a retrospective study, recruiting 88 outpatients consecutively admitted in a 7-month period (from January to July 2017) to the San Gerardo Hospital Outpatient Clinic for Anxiety and Depression (Valutazione Ansia DEpressione nella MEdicina di Comunità Unità di Monza - VADEMECUM) and treated with an antidepressant therapy. San Gerardo University Hospital of Monza covers a comprehensive
range of medical and surgical inpatient and outpatient services, serving a catchment area of about 320,000 inhabitants. Data collection was based on a retrospective review of charts and clinical records. Eligible subjects suffered from Depressive Disorder (n=28), Anxiety Disorder (n=14), Adjustment Disorder (n=32) and other diagnosis (n=14). We collected information on age, gender, severity of depressive symptoms (according to MADRS Montgomery-Åsberg Depression Rating Scale), number of follow-up visits, concurrent psychotherapy, work-related distress, metabolic comorbidities, additional treatments with anxiolytics, antipsychotics or mood stabilizers. Thus, we conducted an analysis of demographic and clinical data comparing outpatients treated with vortioxetine with those treated with sertraline, citalopram, escitalopram and paroxetine. Univariate analyses were carried out. Student’s t test was performed for normally distributed continuous data. Chi-Square and Fisher’s Exact tests were used for categorical variables. Due to the exploratory nature of this study, statistical significance was set at p <0.10.

Results

Subjects had a mean age of 46.3 years and a female to male ratio of 3:1. Work related distress was observed in 33% of outpatients. Mean MADRS score was 20.13 +/- 9.72, mean number of follow-up visits to the outpatient service for each subject was 2.56 +/- 2.36. Most common diagnosis was Adjustment Disorder (36% of outpatients), followed by Depressive Disorder and Anxiety Disorder (Table 1). Among subjects, 26 outpatients were treated with sertraline, 19 with citalopram, 17 with escitalopram, 15 with paroxetine and 11 with vortioxetine (Figure 1). Outpatients treated with vortioxetine required less additional treatments with anxiolytics, antipsychotics and/or mood stabilizers (p=0.07) (Table 2). In particular, anxiolytic prescription was significantly lower in outpatients treated with vortioxetine as compared with those treated with citalopram (p<0.01), escitalopram (p=0.05) and sertraline (p=0.08). Moreover, our data showed that outpatients treated with vortioxetine are more likely to have depressive disorders (p=0.10) (Table 2). No other differences were found, considering age, gender, concurrent psychotherapy, MADRS scores, metabolic comorbidities, and number of follow-up visits.

Discussion

Multimodal action of vortioxetine suggests a different pharmacological profile as compared with other antidepressants (11). Considering vortioxetine increasing spread in clinical practice, it is useful to better understand its pharmacological mechanism, in order to identify which clinical characteristics could mainly benefit of this antidepressant treatment. We found a lower use of additional psychopharmacological therapies (anxiolytic, mood stabilizers or antipsychotics) in subjects treated with vortioxetine, as compared with other traditional antidepressants. In particular, subjects on vortioxetine treatment showed less frequent association with benzodiazepines therapy. An hypothesis could be that vortioxetine is effective in treating anxious symptoms. In addition, we assume that vortioxetine may be preferred in those patients suffering from depression, with less or marginal anxious symptoms. This is also suggested by an higher frequency of depressive disorder diagnosis in patients treated with vortioxetine. No significant differences were found in symptoms severity comparing different antidepressant agents. Although this study provides interesting preliminary data about subjects on vortioxetine treatment, it should been considered that several limitations, including small sample size, exploratory nature, and retrospective analysis, reduce the quality of evidence. Future research should be based on adequately powered studies conducted in real-world settings.

Conflict of interests

The Authors declare no conflict of interests regarding the publication of this paper. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Table 1. Demographic and clinical data.

<table>
<thead>
<tr>
<th>Tot (N=88)</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46.3 +/- 11.5</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>66</td>
<td>75%</td>
</tr>
<tr>
<td>Psychoterapy</td>
<td>19</td>
<td>22%</td>
</tr>
<tr>
<td>Work-related distress</td>
<td>29</td>
<td>33%</td>
</tr>
<tr>
<td>Admissions</td>
<td>2.6 +/- 2.4</td>
<td></td>
</tr>
<tr>
<td>MADRS T0</td>
<td>20.1 +/- 9.8</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 = Depressive disorders</td>
<td>28</td>
<td>32%</td>
</tr>
<tr>
<td>2 = Adjustment disorders</td>
<td>32</td>
<td>36%</td>
</tr>
<tr>
<td>3 = Anxiety disorders</td>
<td>14</td>
<td>16%</td>
</tr>
<tr>
<td>4 = Others</td>
<td>14</td>
<td>16%</td>
</tr>
<tr>
<td>Additional treatments</td>
<td>63</td>
<td>72%</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>4</td>
<td>5%</td>
</tr>
<tr>
<td>Anxyolitics</td>
<td>61</td>
<td>69%</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>9</td>
<td>10%</td>
</tr>
<tr>
<td>Metabolic comorbidities</td>
<td>14</td>
<td>16%</td>
</tr>
<tr>
<td>TOT</td>
<td>88</td>
<td>100%</td>
</tr>
</tbody>
</table>
Treatment with vortioxetine in outpatients with anxiety and depressive disorders: a retrospective analysis

Table 2. Comparison between vortioxetine and other antidepressants.

<table>
<thead>
<tr>
<th></th>
<th>Vortioxetine therapy N = 11</th>
<th>Other antidepressant therapy N = 77</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>48.92 +/- 9.99</td>
<td>45.88 +/- 11.69</td>
<td>ns</td>
</tr>
<tr>
<td>Female</td>
<td>72.7%</td>
<td>75.3%</td>
<td>ns</td>
</tr>
<tr>
<td>Psychotherapy</td>
<td>27.3%</td>
<td>20.8%</td>
<td>ns</td>
</tr>
<tr>
<td>Work related distress</td>
<td>27.3%</td>
<td>33.8%</td>
<td>ns</td>
</tr>
<tr>
<td>Number of admissions</td>
<td>2.91 +/- 3.14</td>
<td>2.51 +/- 2.25</td>
<td>ns</td>
</tr>
<tr>
<td>MADRS T0</td>
<td>21.45 +/- 8.91</td>
<td>20.02 +/- 9.50</td>
<td>ns</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive disorders</td>
<td>54.5%</td>
<td>28.6%</td>
<td>0.10</td>
</tr>
<tr>
<td>Adjustment disorders</td>
<td>18.2%</td>
<td>39.0%</td>
<td>ns</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>18.2%</td>
<td>15.6%</td>
<td>ns</td>
</tr>
<tr>
<td>Other disorders</td>
<td>9.1%</td>
<td>16.9%</td>
<td>ns</td>
</tr>
<tr>
<td>Additional treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>9.1%</td>
<td>3.9%</td>
<td>ns</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>36.4%</td>
<td>74%</td>
<td>0.03</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>18.2%</td>
<td>9.1%</td>
<td>ns</td>
</tr>
<tr>
<td>Metabolic comorbidities</td>
<td>18.2%</td>
<td>15.6%</td>
<td>ns</td>
</tr>
</tbody>
</table>

MADRS, Montgomery-Asberg Depression Rating Scale; ns, not significant.

References

1. Vermani M, Marcus M, Katzman MA. Rates of Detection of Mood and Anxiety Disorders in Primary Care: A Descriptive, Cross-Sectional Study. The Primary Care Companion to CNS Disorders. 2011; 13(2).


Problem gambling and physical health: an observational study

L. Owen1
N. Smith1
R. Santacroce2
Henrietta Bowden-Jones1

1 National Problem Gambling Clinic, Central North West London NHS Foundation Trust, London, UK
2 Department of Neuroscience, Imaging, Clinical Sciences, University “G. d’Annunzio”, Chieti-Pescara, Italy

Address for correspondence:
Henrietta Bowden-Jones
National Problem Gambling Clinic,
Central North West London NHS Foundation Trust
London, UK
Tel.: +44 (0)20 7381 7722
E-mail: h.bowdenjones02@imperial.ac.uk

Abstract

Introduction: Problem gambling is known to be associated with a range of mental, behavioural and social difficulties. There is emerging evidence that an association exists between problem gambling and adverse physical health problems, but this has not been assessed so far in a European setting. This study aims at evaluating self-reported physical health complaints within a cohort of problem gamblers in the United Kingdom.

Methods: Self-reported health conditions and medication usage were recorded in 316 clients referred to the National Problem Gambling Clinic (London) between May 2008 and July 2010.

Results: 36.1% of the participants reported some physical complaint, with 71 individuals (22.5%) classified as having a chronic health complaint (CHC). The most commonly reported physical health complaint was pain (N=13) and the most commonly reported diagnosis was diabetes (N=19). The prevalence of some conditions (e.g., diabetes, HIV) was higher than the national UK prevalence, while others (e.g., hypertension) were lower, but probably under-reported.

Conclusions: Decreased health functioning may be due more to the risk factors within the gambling environment rather than gambling itself (e.g., smoking, unhealthy diet, cheap alcohol consumption). The sustained stress of gambling may also be responsible for the development of physical health conditions. A visit to the Problem Gambling Clinic may be the only contact with the NHS for some clients: it is therefore extremely useful to perform a global assessment in order to identify and understand possible physical conditions and to enhance their motivation to seek treatment.

KEY WORDS: gambling disorder, health, assessment.

Introduction

Gambling has not been perceived as a matter of public health for a long time (1, 2). The practice of gambling is a transversal phenomenon, common to all cultures and ages; in different socio-historical contexts it has often been considered negatively, as sinful, illegal or crime-related (3), but not as an illness. It took until the 1980s for the introduction of problem gambling, or pathological gambling (PG), in the third edition of the Diagnostic and Statistic Manual of Mental Disorders (DSM-III): for the first time, gambling was considered as a disorder associated to a loss of control over the behaviour and therefore included among impulsive control disorders (4). PG prevalence is estimated around 0.8-2.5% in general population (5), but it appears to be extremely higher in samples with psychiatric and drug-related pathologies (6).

In scientific literature, problem gambling is correlated with a range of other mental and behavioural disorders: alcohol and substance misuse (7); behavioural addictions (8); mood disorders (4, 9), anxiety disorders (10), personality disorders (11), high rates of suicidality (12), and social difficulties such as homelessness (13). There is also evidence of an association between PG and adverse physical health conditions. DMS-IV-TR as well noted that pathological gamblers “may be prone to developing general medical conditions that are associated with stress e.g. hypertension, peptic ulcer disease and migraine” (14). An early study by Bergh and Kuhlhorn (15) investigated social, psychological and physical health consequences of PG in a sample of Swedish gamblers. Physical issues resulted to be underestimated by the patients in comparison to social and psychological problems, but the rates of fatigue, influenza, headaches, gastric pain and nausea were higher in pathological gamblers than general population. Similarly, Larimer (16) highlighted how problem gamblers...
experienced high prevalence of many physical symptoms, such as fatigue, insomnia, minor respiratory ailments, intestinal distress, migraine headaches, high blood pressure and cardiovascular disease. Between 2001 and 2002, in the USA 43,093 adults were evaluated by the National Epidemiological Survey on Alcohol and Related Conditions: this was the first study to rigorously investigate the association between physical health and pathological gambling. The researchers found that diagnoses of tachycardia, angina, cirrhosis and other liver diseases were significantly associated with pathological gambling, whilst conditions such as arthritis, and gastritis were higher in pathological gamblers than non-gamblers (17). In the following years, a number of Authors have pointed out the association between PG and physical health conditions (18-20), underlining the need for a more accurate screening of these disorders to provide more comprehensive treatment options. The British Gambling Prevalence Survey is conducted periodically to evaluate the rates of gambling and problem gambling in the United Kingdom. In 2010, the survey reported that problem gamblers were most likely to be male, unemployed, in poor health and have a parent who had gambling problems. The Authors concluded that gambling is a potential health issue and that medical and health professionals need to be aware of gambling-related health problems and develop effective strategies to target them (21). This paper aims at reporting the incidence of physical health complaints in a group of problem gamblers in the United Kingdom.

Methods

Participants
A total of 316 clients referred to the National Problem Gambling Clinic (London, UK) has been assessed between May 2008 and July 2010. All subjects reported a gambling problem, as diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria for pathological gambling. An initial assessment was carried out by a clinician in the form of a semi-structured interview with standardised measures, employed to assess problem gambling and other associated issues. Questionnaires were handed to clients or, if necessary, read out and completed in session. Open-ended questions were asked on a number of gambling and non-gambling indices, including current and previous medical complaints.

Measures

Problem Gambling Severity Index (PGSI)
The PGSI is part of the Canadian Problem Gambling Index (22). It comprises nine questions asking about gambling in the previous 12 months. Responses are scored on a 0-3 Likert scale from “Never” to “Almost always”. Scores of 8 or above are indicative of problem gambling and possible loss of control.

Patient Health Questionnaire (PHQ-9)
The PHQ-9 is a nine-item measure for evaluating depression and monitoring treatment (23). Each of the nine questions is related to a diagnostic criterion for depression according to DSM-IV, occurred in the 2 weeks prior to assessment. Responses are scored on a 0-3 Likert scale from “not at all” to “nearly every day”. PHQ-9 scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depression.

Generalised Anxiety Disorder Scale (GAD-7)
The GAD-7 is a seven-item measure used for screening and monitoring generalised anxiety disorder (24). The questions are focused on anxiety symptoms occurred over the previous 2-week period. Responses are scored on a 0-3 Likert scale from “not at all” to “nearly every day”. 5, 10 and 15 are the cut-off scores for mild, moderate, and severe levels of anxiety, respectively.

Subjective ratings
The subjects were asked to rate their own physical and psychological health, and assess their quality of life. Responses were coded on a 0-20 scale from “poor” to “good”. These scales mimic those present in the Treatment Outcome Profile used by the National Treatment Agency in the UK to monitor the outcomes of drug treatment.

Procedure
Data analysed for this study derived from assessments conducted between May 2008 and July 2010. Any physical health complaint was recorded, and it was registered if it currently represented an issue for the subject. Physical health complaints included minor ailments, injuries and chronic illnesses or physical symptoms; data was rated and agreed by two clinicians. Specifics on chronic health complaints and illnesses were further gleaned from the assessments.

Results
Data were collected from 316 subjects who had been assessed at the National Problem Gambling Clinic between May 2008 and July 2010. The mean age of the sample was 37.6 (± 10.9); 96% of the participants were male. Race-ethnicity categories were “White” (71.5%), “Asian” (8.5%), “Black” (4.4%), “Mixed” (3.2%) and “Other” (5.7%). 114 out of 316 participants (36.1%) reported some physical complaint, with 86 (27.2%) reporting this to be current at the time of assessment. 71 individuals (22.5%) were classified as having a Chronic Health Complaint (CHC).

Table 1 shows figures for specific CHCs reported by assessed individuals. The “other” category (N=7) included endometriosis, genetic muscle disorder, balanitis, chronic fatigue syndrome, chronic obstructive pulmonary disease, hyperthyroidism and hepatitis C.
Associations between reported CHCs and demographic, gambling and associated difficulties are presented in Table 2.
No significant differences were observed in CHCs prevalence for gender and ethnic category variables.

**Discussion and recommendations**

The above-presented findings highlight that the most frequently reported diagnosed condition within this cohort is diabetes (6%). This rate appears to be higher than the national UK prevalence of diabetes (4.45% in 2012) (25). Considering the serious health implications of this disease, clinicians are strongly urged to establish links with diabetes charities and organisations, in order to facilitate easy onward referral for those clients who may neglect their diabetic condition. The prevalence of HIV in the evaluated group of gamblers (1.3%) is also significantly higher than the national UK prevalence, which stands at 0.3% (26). HIV infection risks should therefore be carefully assessed, in order to refer non-treated patients to HIV treatment and care services, and to ensure an adequate support to patients who are already taking antiretroviral therapy. Gamblers also have higher prevalence of arthritis (2.2% among the sample, 0.4% UK national prevalence) (27). This should be considered by the gambling treatment team as affecting treatment prognosis: the sedentary nature of gambling may appeal to an arthritic client whose movement may be limited. In light of this, treatment involving sessions on increasing activity levels may be inappropriate for patients with arthritis, and should be adapted to accommodate their physical health needs.

Several of the other diagnoses reported by the participants are instead lower than national UK prevalence rates, e.g. hypertension (4.1% in our sample versus

<table>
<thead>
<tr>
<th>Variable</th>
<th>Yes</th>
<th>No</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44.3(10.9)</td>
<td>35.6 (10.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PGSI</td>
<td>19.5 (5.3)</td>
<td>18.2 (4.8)</td>
<td>.086</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>14.1 (6.5)</td>
<td>11.4 (6.5)</td>
<td>.002</td>
</tr>
<tr>
<td>GAD-7</td>
<td>11.5 (6.0)</td>
<td>9.2 (5.7)</td>
<td>.004</td>
</tr>
<tr>
<td>Psychological health</td>
<td>8.0 (4.7)</td>
<td>9.3 (4.7)</td>
<td>.046</td>
</tr>
<tr>
<td>Physical health</td>
<td>10.3 (4.7)</td>
<td>12.6 (4.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Quality of life</td>
<td>7.5 (5.2)</td>
<td>9.1 (5.3)</td>
<td>.027</td>
</tr>
</tbody>
</table>
an UK prevalence of 31.5% in men and 29.0% in women) (28). This appears to be surprising, as gambling is known to be associated with high levels of stress (29) which in turn has been linked to hypertension (30). The low levels of these diagnoses may suggest an under-reporting of medical conditions at the time of assessment. Assessment at the Gambling Clinic is primarily focused on gambling behaviour, and a client may be so intent on providing information on the presenting gambling problem that he/she may neglect to report diagnosed medical conditions, or misunderstand the relevance to do so. The prevalence of diabetes, HIV and arthritis and other conditions may therefore also be higher than reported. Clinicians involved in gambling treatment should then pay more attention and spend more time in discussing diagnosed health conditions with the client and exploring health services and resources used.

Decreased health functioning may be due more to the risk factors within the gambling environment rather than the gambling itself; examples are the health effects of smoking, or the potential health repercussions linked to readily available cheap alcohol and junk food. Clients may be unaware of, or chose to ignore, the health impacts associated with these issues. Weight problems, asthma, high cholesterol, diabetes and cardiac problems are among the conditions reported within this study, and all may have known links with the outlined risk factors (17). Psycho-education session should be included in the treatment plan for gamblers, to raise awareness on lifestyle risk factors (e.g smoking; unhealthy eating) and their adverse consequences on physical health.

The sustained stress of gambling can lead to the development of physical health conditions (29) such as sleep disturbances, migraines, gastric problems (e.g. irritable bowel syndrome) and pain (e.g chest pain), all reported within this cohort of problem gamblers. Gambling-related stress experienced by the patient during treatment delivery may impact on his hers ability to receive and retain treatment information: it would be beneficial to practice relaxation with clients who present with increased levels of stress prior to the session commencing.

For some clients, a visit to the Problem Gambling Clinic is often the only contact with the National Health System: personal physical health may not be considered important if compared to gambling-related issues, and therefore may be neglected. The recording of self-reported physical health complaints is an important step of patients assessment, in order to gather information on pre-diagnosed conditions. Results show that “pain” was the most frequently recorded physical health complaint. Pain may have multiple causes and it may be beneficial to discuss its nature and severity. Clinicians have a role to play in identifying and understanding the physical issues that the client presents, and should enhance their motivation to seek treatment. Discussions on the benefits of contacting a physician and some brief education on the possible causes of pain (or other health complaints) is suggested. Clinicians should discuss with the client the potential obstacles that could arise in seeking medical treatment, and help making plans to overcome them, such as offering to book an appointment and writing detailed information on the client’s behalf. The use of motivational interviewing skills (31) would be beneficial in these circumstances. An ideal situation would involve a physician working within the Gambling Clinic for immediate consultation with clients reluctant to pursue the conventional primary care pathway.

Medications used by the client should also be carefully assessed and considered when delivering treatment. Medication use in this study is possibly under-reported, as many clients find it difficult to recall complex drug names, and assessment forms often contained a reported diagnosis but no concurrent medication. An appropriate collection of these data may be crucial for designing an adequate therapeutic path; for example, a number of psychotropic medications have adverse side effects (e.g., antipsychotics may cause blurred vision, dizziness, drowsiness and muscle spasms; mood stabilisers are reported to cause a loss of co-ordination, seizures, blackouts, confusion and fatigue) (32); such side effects may obviously impact on treatment prognosis. Different therapeutic options are now available for the treatment of PG (33): possible interactions with other ongoing therapies should be evaluated in order to choose the safer combination and to reduce synergic adverse effects. It is recommended that medication use is discussed in detail with the client and appropriate session times are planned around this; for example, clients taking sedative medications may benefit from an afternoon appointment, when they may be more alert.

Limitations and considerations

This research focused on one particular cohort, and therefore the findings may not be representative of all groups of problem gamblers. A significant gender bias exists within this sample; gambling has predominantly been a male domain, but although the number of female gamblers has increased in recent years (21), they may be reluctant to seek treatment due to the stigma, shame and belief that it is a male activity. Childcare issues have also been suggested for low treatment seeking rates (34). A further limitation may be related to the relatively young average age of this cohort. Many illnesses may not manifest themselves until a later age. Further research could explore relationships between physical health complaints/diagnoses and age of problem gambler.

Moreover, the data relied on self-reported diagnoses, which were not independently confirmed by a medical professional, resulting in potential inaccuracy of diagnostic data. Similarly, a self-appraisal of an individual’s health is not necessarily congruent with actual
functioning. The subjective nature of self-reported physical health complaints may be a “snapshot” rather than an ongoing physical health problem. The need for further exploration of the reported complaint is necessary at the time of assessment.

Conclusions

The paper outlines self-reported physical health complaints and diagnoses in a cohort of problem gamblers, providing recommendations for service improvement. The data will act as a baseline to inform future treatment within the Problem Gambling Clinic, taking into account the physical health needs of the clients, along with other adverse effects known to be associated with gambling. Recommendations include:

- Psycho-education (stress/diet/alcohol consumption) and relaxation to be incorporated into sessions.
- Reliable recording processes at assessment.
- Clear understanding of client medication use.
- Improvement of links with primary care services and clear onward referral pathways.

Performing a global assessment to identify and understand possible physical conditions is an essential step for providing better care to patients, treating them globally and not only in relation to their gambling behaviour.

References
